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Systematic Review

Ivermectin for Prophylaxis and Treatment of COVID-19: A Systematic Review and Meta-Analysis

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Abstract: Background. Ivermectin has received particular attention as a potential treatment for COVID-19. However, the evidence to support its clinical efficacy is controversial. Objectives. We undertook a new systematic review of ivermectin for the treatment and prophylaxis of COVID-19, including new primary studies, outcomes other than mortality, and grading the quality of the available evidence following the Cochrane guidance for methodology. Methods. We searched electronic databases, repository databases, and clinical trial registries (up to June 2021). The measure of treatment effect was risk difference (RD) with 95% confidence intervals (CIs). The GRADE system was used to assess the certainty of the evidence. Results. The review includes 11 RCTs (2436 participants). The certainty of the available evidence was quite low or very low due to risk of bias, inconsistency, and imprecision. When the analysis was limited to patients with baseline mild or moderate disease (8 reports, 1283 patients), there were no differences in mortality between ivermectin and control groups (low level of certainty); in patients with baseline severe diseases (3 reports, 304 patients), the use of ivermectin significantly decreased mortality compared to the controls (RD −0.17; 95% CIs, −0.24/−0.10; $p = 0.00001$; low level of certainty). In terms of disease progression (to severe pneumonia, admission to intensive care unit, and/or mechanical ventilation), the results were much the same. At day 14, the rate of patients with a negative RT-PCR test was 21% higher (from 5 to 36% higher) for ivermectin recipients than it was for the controls (low quality of evidence). Three studies (736 subjects) indicated that prophylaxis with ivermectin increased the likelihood of preventing COVID-19 compared to controls (low quality of evidence). Serious adverse events were rarely reported. Conclusions. There is limited evidence for the benefit of ivermectin for COVID-19 treatment and prophylaxis, and most of this evidence is of low quality. Further evidence is needed to fine-tune potential indications and optimal treatment protocols for ivermectin as a treatment for COVID-19.

Keywords: ivermectin; SARS-CoV-2; COVID-19; systematic review; meta-analysis

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1. Background

Several drugs have been considered for the treatment of SARS-CoV-2, and various unconventional treatments have been hailed as potential cures for COVID-19 [1–4]. One of the latest putative silver bullets against COVID-19 is ivermectin [5–7]. Apart from its invaluable therapeutic role in parasitic disease such as onchocerciasis and strongyloidiasis [8], there is also an increasing body of evidence showing the potential of ivermectin as an antiviral agent [9–12]. Recently, Caly et al. reported on the antiviral activity of ivermectin against SARS-CoV-2 [13]. In addition to its antiviral activity, ivermectin has proven to have anti-inflammatory effects [14,15]. Although the basis of its anti-inflammatory activity remains unclear, it has been suggested that this phenomenon is closely related to the clinical utility of ivermectin in the cytokine storm phase of COVID-19 [16].

In the past year, ivermectin has received special attention as a potential drug for the treatment and prophylaxis of COVID-19. Indeed, a number of clinical studies have been conducted in various countries, and there is a remarkable number of trials registered with ClinicalTrials.gov and with other clinical trials registries [6]. Recently, the number of primary studies and systematic reviews/meta-analysis focusing on ivermectin for the management of COVID-19 has increased substantially [6,8,17,18]. However, the evidence of the clinical efficacy of ivermectin is controversial [19]. Some of these reviews conclude that ivermectin reduced mortality compared to the standard treatment, but no other outcomes (clinical or virological) were analyzed [6,17,18]. In the systematic reviews available, we observed variability regarding the types and number of studies selected and included, as well as differences in the eligibility criteria and statistical methods used; even more importantly, the assessment of the methodological quality of the studies included and of the quality of evidence, key methodological procedures when conducting systematic reviews, was carried out infrequently with the potential for spurious or fallacious findings [20]. Therefore, we undertook a new systematic review of ivermectin for the treatment and prophylaxis of COVID-19, including new primary studies, outcomes other than mortality, and grading the quality of the available evidence following the Cochrane guidance for methodology.

2. Materials and Methods

This systematic review was conducted according to recommended PRISMA checklist guidelines (Supplementary Material) [21]. The protocol is registered on PROSPERO (registration number CRD42021256414).

2.1. Search Strategy

A computer-assisted literature search of the MEDLINE (through PUBMED), EMBASE, SCOPUS, OVID, and Cochrane Library electronic databases was carried out (latest search 1 June 2021) to identify clinical trials for the use of ivermectin for COVID-19. A combination of the following text words and MeSH terms was used: COVID-19/SARS- CoV-2 AND ivermectin. We also searched preprint repository databases (medRxiv, bioRxiv) and clinical trial registries (clinicaltrials.gov, who.int/clin.gov, accessed on 1 June 2021) for study details and study results. In addition, we checked the reference lists of the most relevant items (original studies and reviews) in order to identify potentially eligible studies not captured by the initial literature search.

2.2. Study Selection and Inclusion Criteria

Studies were selected independently by two reviewers (I.P. and M.C.), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (F.M.). This review included RCTs published in full or as preprint. Observational non-RCTs were not considered. Studies evaluating both outpatients and inpatients (stratified by the severity of COVID-19) were included.

2.3. Types of Intervention

The investigation group included patients with confirmed COVID-19 receiving ivermectin ± standard treatment (ST) as defined in the individual study; the control group included patients receiving ST and/or placebo (Tables 1 and S1).

Table 1. Main characteristics of included studies.

Study [Reference]	Patient Characteristics	Design	Interventions	Outcomes	Follow-Up	Main Results
Ahmed 2021 [22]	72 hospitalized patients. Mean age 42 years; 54% female. The duration of illness before assessment was an average of 3.83 days.	A randomized, double-blind, placebo-controlled trial	3 groups: oral ivermectin alone (12 mg once daily for 5 days), oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days), and a placebo control group.	Time required for virological clearance; remission of fever and cough within 7 days; failure to maintain a SpO2 > 93% despite oxygenation; days on oxygen support; duration of hospitalization.	14 days	Clinical symptoms of fever, cough, and sore throat were comparable among the three groups. Virological clearance was earlier in the 5-day ivermectin treatment arm when compared to the placebo group, but this was not the case for the ivermectin + doxycycline arm.
Chaccour 2021 [23]	24 patients (median age, 26 years (IQR 19–36 in the ivermectin and 21–44 in the controls); 12 (50%) women; 100% had symptoms at recruitment, 70% reported headache, 62% reported fever, 50% reported general malaise and 25% reported cough).	A pilot, double-blind, placebo-controlled, RCT	Ivermectin (400 mcg/kg) single oral dose (12 pts) or placebo (12 pts).	% of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment; viral load at days 4, 7, 14, and 21 post-treatment; % pts. with fever and cough at days 4, 7, 14, and 21 post-treatment; % pts. progressing to severe disease or death during the trial; % pts. with seroconversion at day 21 post-treatment; drug-related adverse events.	28 days	At day 7, there was no difference in the proportion of PCR-positive patients. The ivermectin group had non-statistically significant lower viral loads at day 4 and day 7 post-treatment.
Chahla 2021 [24]	234 healthcare personnel (medical personnel, nurses, kinesiologists) and also administrative and cleaning personnel. The median age was 38 years (range 22–69). 77.4% of the participants were healthcare personnel.	RCT	The experimental group (117 patients) received ivermectin 12 mg every 7 days, and the control group (117 patients) received iota-carrageenan 6 sprays per day for 4 weeks.	Enrolled subjects completed symptom questionnaires (including reporting any adverse effects of treatment), physical examinations, and COVID-19 nasopharyngeal secretion tests (RT PCR) at each time point.	14 days	The intensive preventive treatment (short-term) with IVER/IOTACRC was able to reduce the number of health workers infected with COVID-19. This treatment also had an effect in preventing the severity of the disease.

Table 1. *Cont.*

Study [Reference]	Patient Characteristics	Design	Interventions	Outcomes	Follow-Up	Main Results
Elgazzar 2020 [25]	600 subjects from 18 years up to 80 years old; 400 symptomatic confirmed COVID-19 patients and 200 healthcare and household contacts.	A multicenter double blind, RCT	Group I: 100 patients with mild/moderate COVID-19 infection received a 4-day course of ivermectin plus standard of care; Group II: 100 patients with mild/moderate COVID-19 infection received hydroxychloroquine plus standard care; Group III: 100 patients with severe COVID-19 infection received ivermectin plus standard care; Group IV: 100 patients with severe COVID-19 infection received hydroxychloroquine plus standard care.	Clinical, laboratory investigations; improvement and/or two consecutive negative PCR tests taken at least 48 h apart; patients presenting with adverse events requiring stoppage of treatment and management of any side effects accordingly.	14 days	Patients receiving ivermectin early reported substantial recovery of laboratory investigations and significant reduction in rT-PCR conversion days. Ivermectin significantly reduced the incidence of infection in healthcare and household contacts up to 2% compared to 10% in the non-ivermectin group.
Hashim 2020 [26]	140 COVID-19 patients at different stages of the disease. All patients were diagnosed by clinical, radiological, and laboratory PCR testing. Mean age of the recruited patients was 48.7 $\pm$ 8.6 year.	RCT	70 COVID-19 patients (48 mild-moderate, 11 severe, and 11 critical patients) treated with 200 ug/kg PO of ivermectin per day for 2–3 days along with 100mg PO doxycycline twice per day for 5–10 days plus standard therapy; the second arm included 70 COVID-19 patients (48 mild-moderate and 22 severe, and 0 critical patients) on standard therapy.	Time to recovery; the progression of the disease; the mortality rate.	1 month	Ivermectin with doxycycline reduced the time to recovery and the percentage of patients who progressed to more advanced stage of disease.

Table 1. *Cont.*

Study [Reference]	Patient Characteristics	Design	Interventions	Outcomes	Follow-Up	Main Results
Lopez- Medina 2021 [27]	476 adult patients with mild disease and symptoms for ≤7 days (at home or hospitalized); the median age of pts. was 37 years (IQR range, 29–48), wherein 231 (58%) were women and 316 (79%) did not have any known comorbidities at baseline.	A double-blind, RCT	Study patients received 300 µg/kg per day of oral ivermectin in solution (200 patients) or the same volume of placebo for 5 days (200 patients). Up to 26 August 2020, the placebo was a mixture of 5% dextrose in saline and 5% dextrose in distilled water, after which placebo was a solution with similar organoleptic properties to ivermectin provided by the manufacturer.	Mortality; time to complete resolution of symptoms; % of patients who developed fever and duration of fever; evaluation of adverse events (AEs) included solicited AEs, AEs leading to treatment discontinuation, and serious AEs.	1 month	Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms.
Mahmud 2021 [28]	400 patients were enrolled and 363 completed follow-up. The mean age of all patients was 40 years, and 59% were men. Most patients presented with fever (300, 75%) or cough (247, 62%). Respiratory distress was noted in 123 (31%) patients at presentation.	RCT, blinded, placebo-controlled	The treatment group (200 patients) received a single dose of ivermectin 12 mg and doxycycline 100 mg, twice daily for 5 days, in addition to standard of care. Standard of care included administration of paracetamol, antihistamines, cough suppressants, vitamins, oxygen therapy according to indication and need, low molecular weight heparin according to indication, appropriate other broad-spectrum antibiotics, remdesivir injection, other antiviral drugs, and other drugs for associated comorbid conditions. The placebo group (200 patients) received placebo in addition to standard of care.	The number of days required for clinical recovery from day 1; secondary outcomes was disease progression through mild, moderate, severe, or death, and the proportion of patients who continued to test positive for COVID-19 on day 14. Adverse events were also recorded.	14 days	Patients with mild-to-moderate COVID-19 infection treated with ivermectin plus doxycycline recovered earlier were less likely to progress to more serious disease and were more likely to be COVID-19-negative by RT-PCR on day 14.

Table 1. *Cont.*

Study [Reference]	Patient Characteristics	Design	Interventions	Outcomes	Follow-Up	Main Results
Niaee 2020 [29]	A total number of 180 mild to severe hospitalized patients with confirmed PCR and chest image tests were enrolled. Average age of the participants was 56 years (45–67), and 50% were women.	RCT, double-blind, placebo-controlled, multicenter phase 2 clinical trial	The participants were randomly allocated to six arms including common regimen based on the Iran Health Ministry (hydroxychloroquine 200 mg/kg twice per day), placebo plus common regime, single dose ivermectin (200 mcg/Kg, 1 pill per day), three low interval doses of ivermectin (200, 200, 200 mcg/Kg, 3 pills in 1, 3 and 5 interval days), single-dose ivermectin (400 mcg/Kg, 2 pills per day), and three high-interval doses of ivermectin (400, 200, 200 mcg/Kg, 4 pills in 1, 3 and 5 interval days).	The radiographic findings, hospitalization (clinical recovery within 45 days of enrolment), low O_2 saturation duration, and clinical outcomes such as mortality and variables of blood samples.	45 days	The decrease in hospitalization and low O_2 saturating terms was significant in ivermectin-treated 1–4 arms compared to the two untreated controls ($p = 0.006$ and $p = 0.025$, respectively). The lowest mortality rate (0%), hospitalization duration (5 days), and duration of low O_2 saturation (2 days) was observed in arm 3 with single dose of 400 mcg/kg ivermectin.
Okumus 2021 [30]	66 patients with severe COVID-19 were enrolled, and 60 completed the study. The mean age of all patients was 58 years for the study group and 66 years for the control group. 70% of the study group were men.	RCT, single-blind phase 3 multicenter clinical trial	The study group received ivermectin 200 mcg/kg/day for 5 days added to the reference treatment protocol (hydroxychloroquine + favipiravir + azithromycin). Patients in the control group were given only reference treatment with three other drugs without ivermectin.	Rate of RT-PCR test negativity; mortality; adverse events; clinical response; changes in clinical and in laboratory parameters.	5 days	At the end of five-day treatment period (primary endpoint), the rate of clinical improvement was 46.7% (14/30) in the study group and 36.7% (11/30) in the control group. Mortality occurred in 6 patients (20%) in the study group and in 9 (30%) patients in the control group.

Table 1. *Cont.*

Study [Reference]	Patient Characteristics	Design	Interventions	Outcomes	Follow-Up	Main Results
Ravikirti 2020 [31]	112 patients with mild-moderate disease. The mean age of pts. was 51 years for the study group and 54 years for the control group. 70% of the study and the control group were men.	RCT, double blind, placebo-controlled trial	Two groups of intervention with ivermectin (12 mg on day 1 and day 2 of admission) or placebo, but in both groups, all patients also received hydroxychloroquine, steroids, enoxaparin, remdesivir, antibiotics, convalescent plasma, tocilizumab, and other drugs.	Negative PCR test at day 6; symptoms status at day 6; discharge status; admission to ICU; need of mechanical ventilation; mortality.	10 days	There was no difference in the primary outcome (negative RT-PCR on day 6) between the two groups. Similarly, there was no significant difference between the two groups in most of the secondary outcome measures. However, while there was no in-hospital mortality in the intervention arm, there were four deaths in the placebo arm.
Shouman 2021 [32]	304 asymptomatic ($\geq$16 yrs) contacts of 76 RT-PCR-confirmed patients,	A RCT, open label	In ivermectin arm, contacts received ivermectin according to body weight on the day of the diagnosis of their index case. The non-intervention group received no treatment. Ivermectin was given at day 1 (diagnosis day) and repeated once more at day 3 (total of two doses).	RT-PCR test for COVID-19, including fever with respiratory symptoms plus or minus others symptoms.	14 days	Fifteen contacts (7.4%) developed COVID-19 in the ivermectin arm, compared to 59 (58.4%) in the non-intervention arm ($p < 0.001$). The protection rate for ivermectin was more prominent in contacts aged less than 60 years old.

2.4. Outcomes

Primary outcomes were overall mortality, progression to severe disease (severe pneumonia, admission to intensive care unit, and/or mechanical ventilation), and serious adverse events. Secondary outcomes included viral clearance and overall occurrence of adverse events. Where available, the outcome measures were reported in different follow-up periods. In studies evaluating prophylaxis, the outcome was efficacy of ivermectin compared to control in preventing COVID-19 among contacts.

2.5. Data Collection and Analysis

The following data were extracted by two reviewers (I.P. and M.C.) independently: first author, year of publication, regimens under investigation, outcome measures, and main results. Measures of treatment effect were mean differences (MD) together with 95% confidence intervals (CIs) for continuous outcome measures and risk differences (RD) for binary outcomes. Disagreement was resolved by consensus and by a third reviewer (F.M.), if necessary.

The study weight was calculated using the Mantel–Haenszel method. We assessed statistical heterogeneity using t^2, Cochran's Q, and I^2 statistics. The I^2 statistic describes the percentage of total variation across trials due to heterogeneity rather than sampling error. In the case of no heterogeneity ($I^2 = 0$), studies were pooled using a fixed-effects model. Where values of I^2 were >0, a random-effects analysis was undertaken.

2.6. Assessment of Risk of Bias in Included Studies

Two review authors (I.P., M.C.) independently assessed the risk of bias of each study included following the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions (Available from www.handbook.cochrane.org, accessed on 18 August 2021) [33,34]. They discussed any discrepancies and achieved consensus on the final assessment. The Cochrane 'risk of bias' tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias.

2.7. 'Summary of Findings' Tables

We used the principles of the GRADE system (Available from www.handbook.cochrane.org, accessed on 18 August 2021) to assess the quality of the body of evidence associated with specific outcomes and constructed 'summary of findings' tables using REVMAN 5.4 (Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020) [35]. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of available data for the main outcomes [36]. The GRADE system defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

We present the following outcomes in the 'summary of findings' table: overall mortality, disease progression, viral clearance, serious adverse events, and rate of infection in prophylaxis studies.

2.8. All Calculations Were Made Using REVMAN 5.4

Subgroup Analyses

We anticipated heterogeneity in the design and reporting of studies and, to deal with heterogeneity, we planned to carry out subgroup analyses considering specific patients or the characteristics of interventions that may have an effect [37]. Therefore, we considered the following sub-group analyses:

- Mortality and disease progression in ivermectin and control group according to baseline clinical conditions (e.g., mild, moderate or severe COVID-19);

- Mortality in ivermectin and control group according to the intervention regimen (ivermectin alone or in combination with other active drugs), and according to ivermectin dosage;
- Virological data according to the observation period (i.e., 10 and 14 days);
- Comparative efficacy of ivermectin in preventing overall COVID-19 and infections stratified by clinical severity.

Once sufficient trials were identified, we planned to carry out a sensitivity analysis comparing the results according to methodological quality (i.e., studies classified as having a 'low risk of bias' versus those identified as having a 'high risk of bias').

3. Results

The search yielded 208 potentially relevant studies (Figure 1, study flow chart).

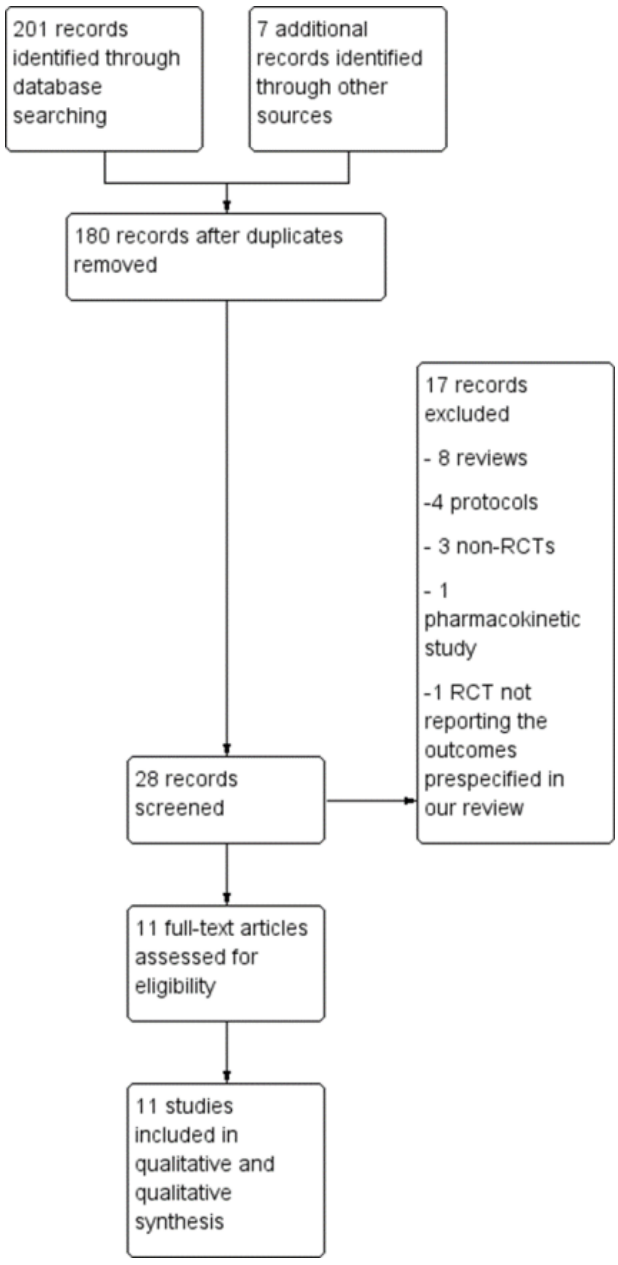

Figure 1. Study flow chart.

A total of 180 reports were excluded after preliminary screening; 28 were deemed potentially eligible, and the full-text was assessed. Seventeenstudies were then excluded (eight reviews [2,3,5–8,15,16], four protocols [37–40], three non-RCTs [41–43], a pharmacokinetic study [44], and a pilot RCT not reporting the predefined outcomes of our review [45]). Hence, 11 studies were available for qualitative synthesis [22–32]. The main features of the studies included are summarized in Tables 1 and S1.

Overall, 2436 individuals were enrolled in the 11 RCTs selected for the review: 1295 received ivermectin and 1141 placebo or other treatment. In three studies, ivermectin was given as prophylaxis [24,25,32], and in nine as treatment [22,23,25–31]. Studies were conducted in Egypt (2); India (1); Argentina (1); Bangladesh (1); Bangladesh and Singapore (1); Spain, Switzerland, and the USA (1); Iraq (1); Iran (1); Colombia (1); and Turkey (1).

3.1. Risk of Bias in Included Studies

Four studies (36%) were with high risk of bias for one or more domains, and all the studies were with unclear risk of bias for 1 or more domains (Figure S1).

3.2. Allocation

We assessed two studies as being with high risk of selection bias due to the randomization by alternation of the two treatments and because the intervention allocations could have been foreseen in advance [26,30]. The reports of three other studies were unclear for random sequence generation and/or allocation concealment, while five studies (45%) were with low risk of selection biases.

3.3. Blinding

Performance bias. Four studies (36%) were reported as open label and were graded as high risk of performance bias (blinding of participants and personnel); four studies (36%) were graded as with unclear risk of performance due to the lack of the information required to come to a judgement about 'high' or 'low' risk of bias related to the blinding of participants and personnel. Three studies were reported as double-blind.

Detection bias. No study provided the information required to come to a judgement about 'high' or 'low' risk of bias related to the blinding of outcome assessors, and were graded as with unclear risk of detection bias.

3.4. Incomplete Outcome Data

Two studies were deemed as having unclear risk of attrition bias because of the lack of information on the number of patients that completed the study, or because a high proportion of enrolled patients (>10%) did not complete the study. The remaining nine studies (81%) were deemed as having low risk of bias.

3.5. Selective Reporting

Selective reporting bias was low in nine studies (81%). One study was deemed to have an unclear risk of bias, and one study with high risk (Table S1).

3.6. Other Potential Sources of Bias

Nine studies were deemed with low risk of other bias, and two studies with unclear risk of other bias.

3.7. Effects of Interventions

A summary of the outcomes reported in the included study is provided in Figure 2 (data and analysis). The outcomes most commonly reported were mortality; disease progression; viral clearance; overall side effects; serious side effects; and, for prophylaxis trials, the rate of infection among contacts.

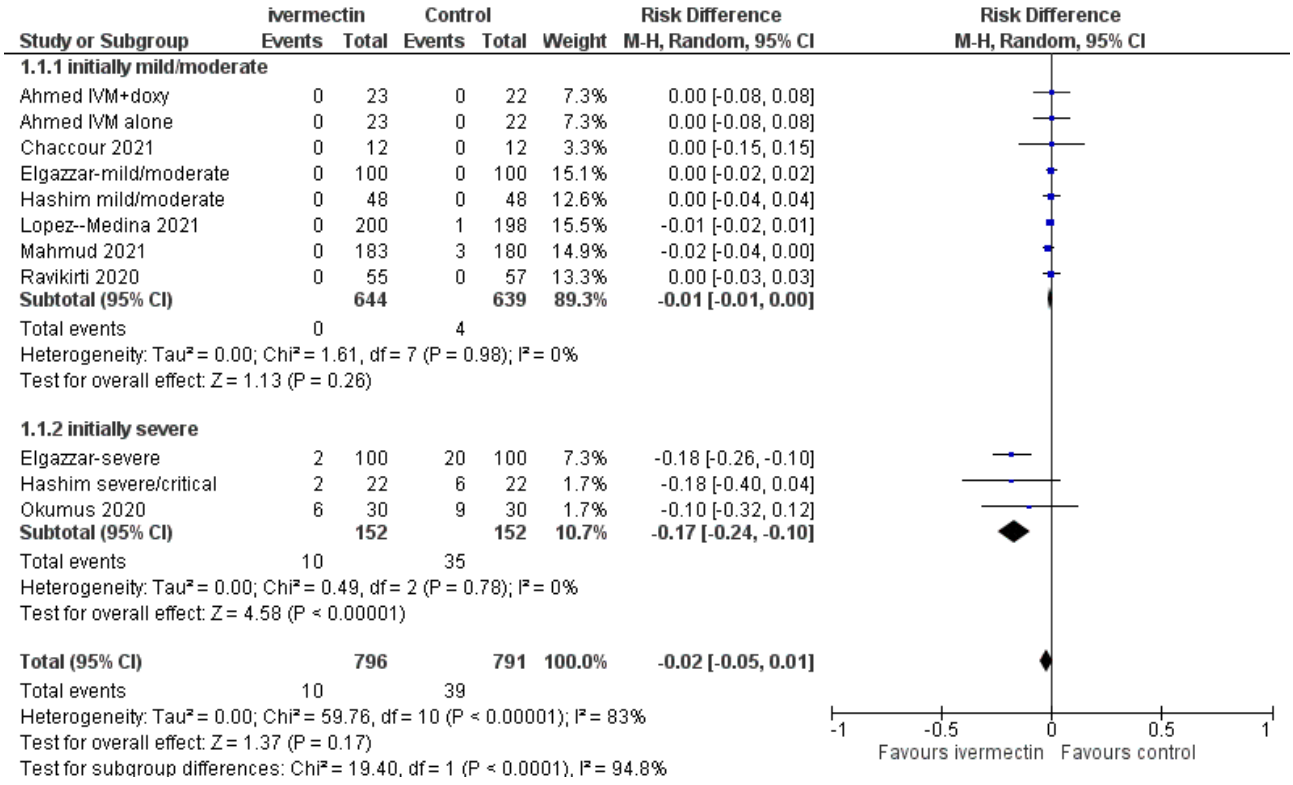

Figure 2. Forest plot of comparison. Outcome: overall mortality according to initial clinical status.

3.8. Mortality

Data on mortality were reported in all nine studies evaluating ivermectin treatment. There were 10 deaths out of 796 patients in the ivermectin group compared to 39/791 in the control group (RD −0.02; 95% CIs, −0.05/0.01; $p = 0.17$) (Figure 2).

In eight studies, mortality was reported according to the severity of COVID-19. When the analysis was limited to studies or a subset of patients with baseline mild or moderate disease (8 reports, 1283 patients), there were no differences in mortality between ivermectin and control groups (RD, −0.01; 95% CIs, −0.01/0.00; $p = 0.26$) (Figure 2). The quality of the evidence was deemed low (downgraded for risk of bias and imprecision) (Table 2, summary of findings table).

When the analysis was restricted to studies or subsets of patients with baseline severe diseases (3 reports, 304 patients) [25,26,30], the use of ivermectin decreased mortality compared to controls (RD −0.17; 95% CIs, −0.24/−0.10; $p = 0.00001$). The quality of the evidence was deemed low (downgraded twice for severe risk of selection biases).

In sensitivity analysis, after the exclusion of the study by Elgazzar et al. [35] in the subset of studies with baseline severe conditions the difference in the occurrence of mortality is not longer favouring ivermectin compared to controls (MD, −0.14 (95% CIs, −0.30/0.02; $p = 0.08$). As in the previous analyses, the certainty of the available evidence remains low.

For the mortality outcome, we carried out subgroup analyses considering the drugs included in the ivermectin regimens and the dosage of ivermectin. In three studies (or subset of patients) [23,27,43], ivermectin was given alone and compared to placebo. In seven studies or subsets of patients [25,26,28–31], ivermectin was given in combination with standard treatment including other active drugs (e.g., doxycycline, azithromycin, remdesivir, steroids, anticoagulants, and others) and compared to controls receiving the same standard treatment. In studies comparing ivermectin to placebo, there was one death (in the control group) out of 467 patients enrolled (RD, −0.00; 95% CIs, −0.02/0.01; $p = 0.48$; moderate quality of evidence; downgraded once for imprecision) (Figure 3).

Table 2. Ivermectin compared with control intervention for COVID-19 treatment or prevention. Patient or population: Patients with COVID-19 for treatment studies; healthcare personnel and household contacts for prevention studies. Settings: outpatients and hospitalized patients. Intervention: ivermectin ± standard treatment. Comparison: standard treatment.

Outcomes	Illustrative Comparative Risks * (95% CI)		Relative Effect (95% CI)	No of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
	Control	Ivermectin				
Mortality according to baseline conditions	**Low-risk population (mild/moderate disease)**		**RD −0.01 (−0.01/0.00)**	**1283 (7)**	⊕⊕⊖⊖ **low** [1]	On average, it is unclear whether or not use of ivermectin compared to control decreases mortality in low-risk population. The average benefit is higher in the high-risk population.
	mortality ranged from 0 to 1.6%	mortality was 1% lower (from 0 to 1% lower)				
	High risk population (severe disease)		**RD −0.17 (−0.24/−0.10)**	**304 (3)**	⊕⊕⊖⊖ **low** [2]	
	mortality ranged from 20% to 30%	mortality was 17% lower (from 10% to 24% lower)				
Viral clearance (% patients)	**At 6–10 days**		**RD 0.10 (−0.12/0.31)**	**430 (5)**	⊕⊖⊖⊖ **very low** [3]	On average, it is unclear whether or not use of ivermectin compared to control decreases rate of patients with RT-PCR negative test after 6–10 days. After 14 days, ivermectin increases rates of pts with negative RT-PCR test compared to control.
	rate of patients with negative RT-PCR ranged from 0 to 46.6 per 100	rate of patients with negative RT-PCR was 10% higher (from 31% higher to 12% lower)				
	At 14 days		**RD 0.21 (0.05/0.36)**	**360 (2)**	⊕⊕⊖⊖ **low** [4]	
	rate of patients with negative RT-PCR ranged from 36 to 80 per 100	rate of patients with negative RT-PCR was 21% higher (from 5% to 36% higher)				
Disease progression (severe pneumonia, admission to intensive care unit, and/or mechanical ventilation) according to baseline conditions	**Low-risk population (mild/moderate disease)**		**RD −0.05 (−0.11 to 0.00)**	**1405 (7)**	⊕⊖⊖⊖ **very low** [3]	On average, it is unclear as to whether or not use of ivermectin compared to control decreases disease progression in the low-risk population. The average benefit is higher in the high-risk population.
	disease progression ranged from 0 to 22 per 100	rate of patients with disease progression was 5% lower (from 0 to 11% lower)				
	High-risk population (severe disease)		**RD −0.09 (−0.16/−0.02)**	**302 (3)**	⊕⊕⊖⊖ **low** [4]	
	disease progression ranged from 30 to 46 per 100	rate of patients with disease progression was 9% lower (from 16 to 2% lower)				
Serious adverse events	serious adverse events ranged from 0 to 2.5 per 100	serious adverse events were 1% higher (from 1% lower to 2% higher)	**RD 0.01 (−0.01/0.02)**	**1428 (6)**	⊕⊕⊖⊖ **low** [1]	Serious adverse events were rarely reported in both ivermectin and control groups.
Prevention of infection in healthcare and household contacts of COVID-19 pts	rate of infection ranged from 10 to 58 per cent	rate of infection was 28% lower (from 61 to 41% lower)	**RD −0.28 (−0.33/−0.23)**	**736 (3)**	⊕⊖⊖⊖ **very low** [5]	Prophylaxis with ivermectin increased the likelihood of preventing COVID-19 compared to controls.

* The assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RD: risk difference. GRADE: working group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate. [1] Downgraded for risk of bias and imprecision (95% CI includes line of no effect); [2] downgraded twice for risk of bias; [3] downgraded for risk of bias, imprecision, and inconsistency (due to heterogeneity); [4] downgraded for risk of bias and inconsistency; [5] downgraded for risk of bias, inconsistency, and indirectness.

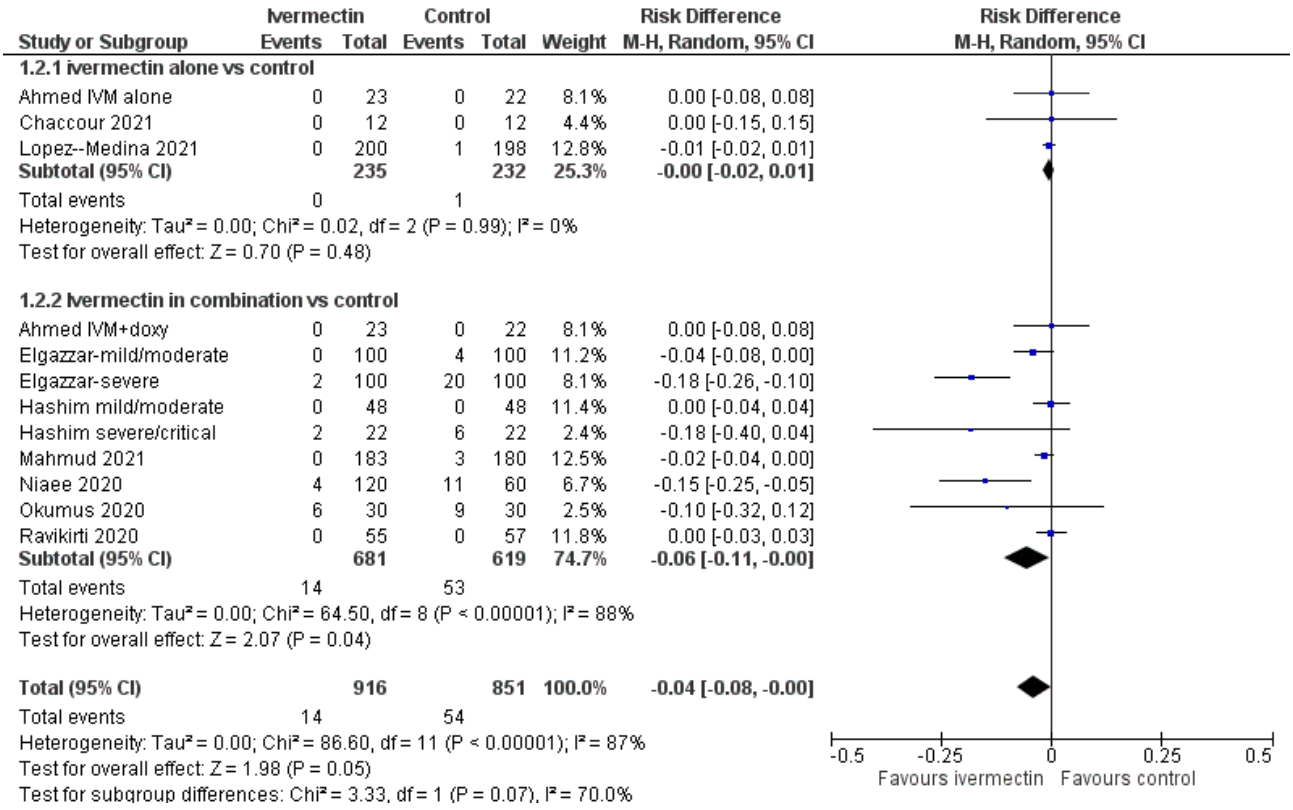

Figure 3. Forest plot of comparison. Outcome: mortality according to ivermectin regimens (ivermectin alone or in combination with 'standard treatment').

In studies comparing ivermectin plus standard treatment vs. standard treatment, there were 14 deaths among 681 patients receiving ivermectin, and 53 deaths among 619 patients receiving standard treatment (RD, −0.06; 95% CIs, −0.11/−0.00; $p = 0.04$; low quality of evidence due to risk of bias and inconsistency). Ivermectin, in single dose or 2–5 daily doses, was used as 400 µg/kg dose in four trials [23,25,27,29], and as 200 µg/kg dose in six trials [23,25,29,31,44,45]. In both cases, there was no difference in the mortality rate between ivermectin recipients and control (Figure S2).

3.9. Virological Outcomes

The rate of patients with negative RT-PCR test was evaluated at 6–10 days and at 14 days (Figure 4, Table 2).

At day 10, ivermectin did not significantly increase the proportion of RT-PCR-negative patients (RD, 0.10; 95% CIs, −0.12/0.31; $p = 0.38$). The GRADE assessment showed very low quality of evidence due to risk of bias, inconsistency, and imprecision. At day 14, the rate of RT-PCR-negative patients was significantly higher among ivermectin recipients compared to controls (RD 0.21; 95% CIs, 0.05/0.36; $p = 0.01$; low quality of evidence due to risk of bias and inconsistency).

3.10. Disease Progression

Disease progression (to severe pneumonia, admission to ICU, and/or mechanical ventilation) was observed less frequently among ivermectin recipients compared to controls (RD, −0.09; 95% CIs, −0.16/−0.02; $p = 0.01$; very low quality evidence; downgraded twice for serious risk of selection biases, and once for inconsistency). The size of the effect was more evident in the high-risk population (severely ill at baseline) (RD, −0.26; 95% CIs, −0.34/−0.17; $p < 0.00001$; very low quality of evidence; downgraded twice for serious

risk of selection biases, and once for inconsistency) compared to the low-risk population (mild/moderate diseases) (RD, −0.05; 95% CIs, −0.11/0.00; $p = 0.07$; low quality evidence due to risk of bias and imprecision) (Figure 5, Table 2).

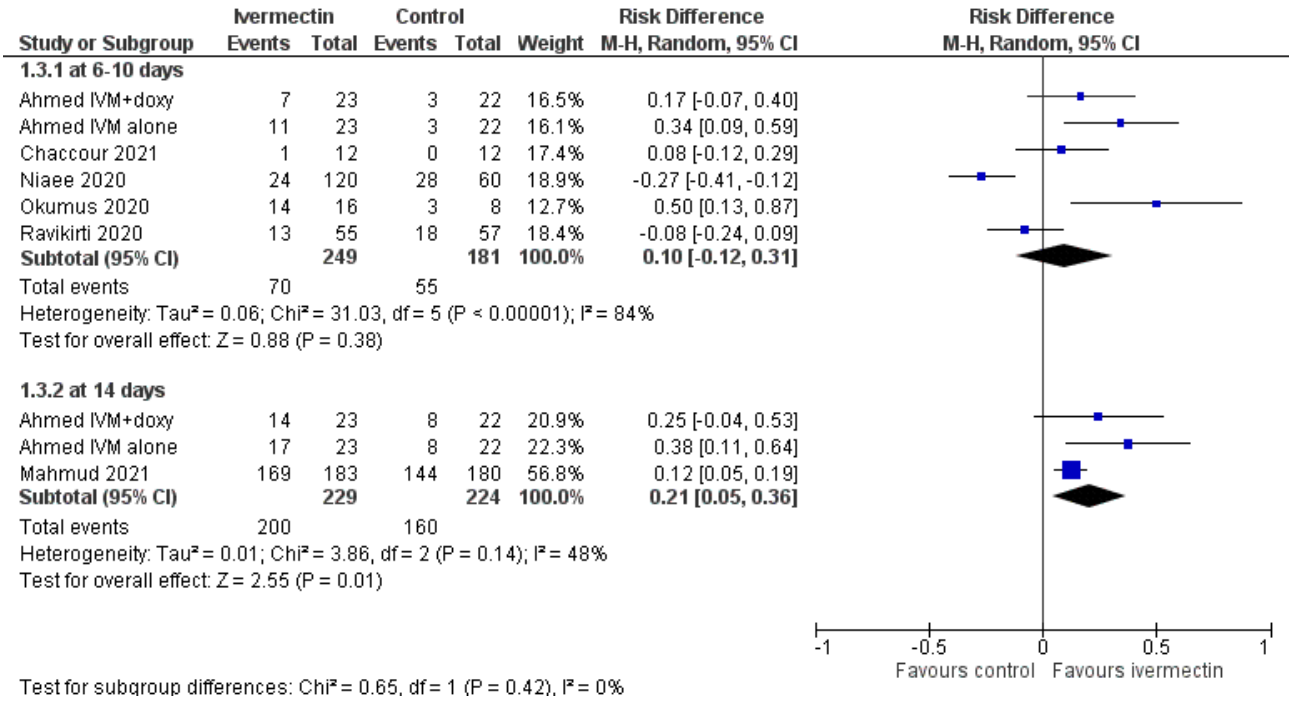

Figure 4. Forest plot of comparison. Outcome: rate of patients with RT-PCR test for COVID-19 negative at days 6–10 and at day 14.

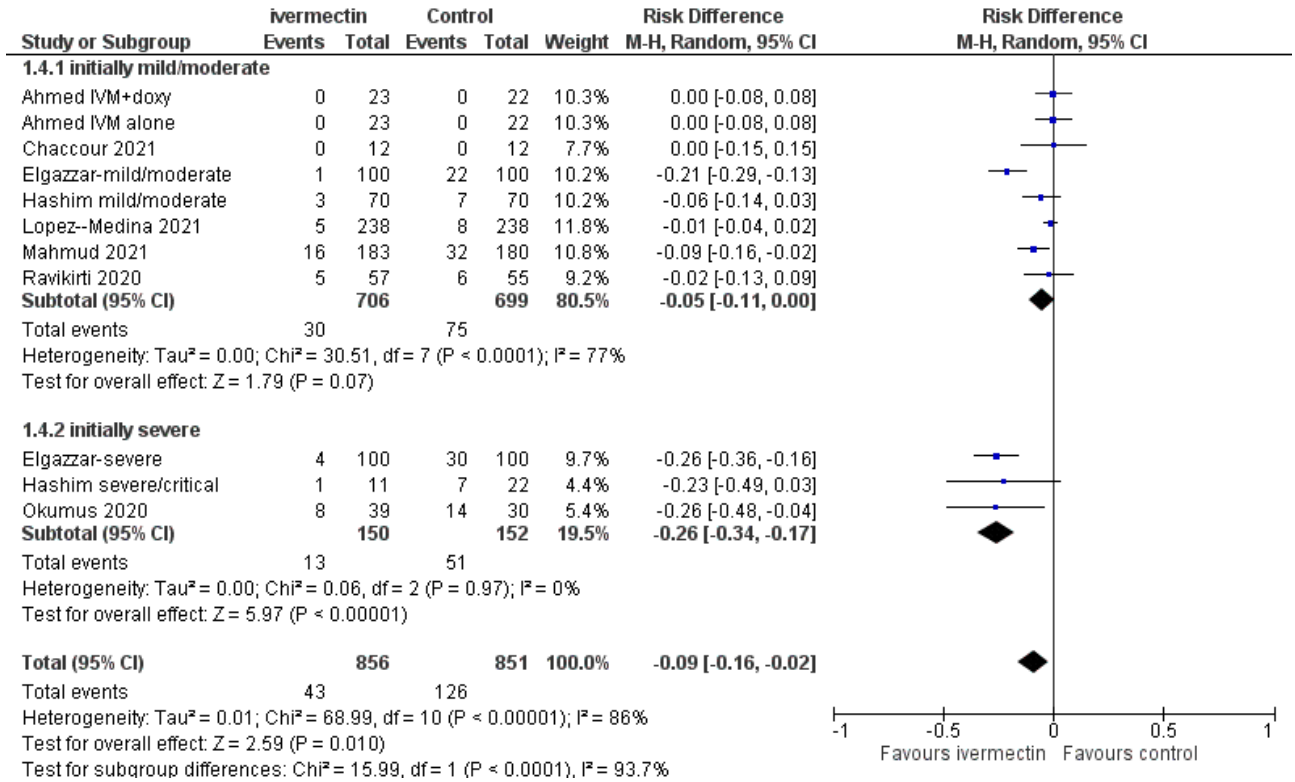

Figure 5. Forest plot of comparison. Outcome: clinical progression according to initial clinical status.

3.11. Adverse Events

Few participants were reported undergoing a serious event in either Ivermectin or control groups (Figure S3). This comparison was graded as low-quality evidence and downgraded once due to risk of bias and once for imprecision (95% CIs include the line of no effect).

Overall side effects were reported in 253 of the 913 ivermectin recipients and 274 of the 811 controls (RD, −0.01/95% CIs, −0.11/0.08; $p = 0.78$) (Figure S3, Table S2).

3.12. Ivermectin for Prophylaxis among Healthcare and/or Household Contacts of COVID-19

Three studies [24,25,32] evaluated the effectiveness of ivermectin prophylaxis compared to no treatment or to topical treatment with carrageenan (an antiviral compound applied locally in the nasal and oral cavity). In one study [32], clinical evaluation was carried out in all subjects, but RT-PCR only in a minority of patients; hence, asymptomatic infections among contacts may have been missed in both groups, rating down the quality of the evidence for indirectness. The incidence of COVID-19 was significantly lower among ivermectin recipients than controls (RD, −0.28; 95% CIs, −0.33/−0.23; $p < 0.00001$; very low quality of evidence; downgraded for risk of bias, indirectness, and inconsistency (Figure S4)). Ivermectin was significantly more effective than control in preventing mild, moderate, and severe infections (Figure S5).

4. Discussion

Other meta-analyses have specifically examined the role of ivermectin for COVID-19 [6,17,18]. One, based on 4 trials and 397 participants, concluded that ivermectin reduced overall mortality and led to a significant clinical improvement compared to the usual therapy, but also highlighted the limitations of these conclusions due to the very low quality of the available evidence [7]. In the other two reviews, overall mortality was the only outcome considered; both studies revealed a significant reduction of the odds of mortality in ivermectin recipients compared to the controls [17,18]. However, there were other methodologic limitations in these two systematic reviews, since no subgroup analysis was carried out to address the heterogeneity observed, and in one review [17], there was no assessment of the methodological quality of included studies. Moreover, the number of studies and participants included in all these reviews was far lower than in our systematic review.

The current review includes 11 RCTs and 2436 participants. Studies were grouped into two main comparisons: (i) ivermectin as treatment of COVID-19; (ii) ivermectin as prophylaxis of COVID-19 in household and/or healthcare personnel contacts with COVID-19 cases. The certainty of the available evidence was quite low or very low, and at best moderate.

Pooled data for ivermectin compared with controls suggest that once the analysis was limited to studies or a subset of patients with baseline mild or moderate disease (8 reports, 1283 patients), there were no differences in mortality between ivermectin and control groups (low level of certainty). When the analysis was restricted to studies or a subset of patients with baseline severe diseases (3 reports, 304 patients), the use of ivermectin significantly decreased mortality compared to controls (low level of certainty). An assessment of low-certainty evidence means that our confidence in the effect estimate is low, and the true effect may be substantially different from the estimate. In subgroup analyses, we found that in studies comparing ivermectin alone to placebo, mortality was comparable: 1 death (in the control group) out of 467 patients enrolled (moderate quality of evidence; downgraded once for imprecision). In studies comparing ivermectin plus standard treatment vs. standard treatment, there were 14 deaths among 681 patients receiving ivermectin, and 53 deaths among 619 patients receiving standard treatment (RD, −0.06; 95% CIs, −0.11/−0.00; $p = 0.04$; low level of certainty due to risk of bias and inconsistency).

The results in terms of disease progression (to severe pneumonia, admission to intensive care unit, and/or mechanical ventilation) were much the same. On average, it is unclear whether or not the use of ivermectin compared to controls decreases disease progression in the low-risk population (very low quality of evidence). These results do not provide a reliable indication of the likely effect, and the possibility that the actual effect will be substantially different is very high. On the other hand, the rate of disease progression was significantly lower in the ivermectin group compared to control, but the quality of the evidence is once again low.

Notably, our data indicate that ivermectin is more active in reducing mortality and clinical progression among severely ill patients, suggesting that the clinical utility of ivermectin may reflect an anti-inflammatory activity of the drug in the late stage rather than an antiviral activity in the early stage of COVID-19. This anti-inflammatory activity has already been demonstrated in animal models of infection and seems to be related to the inhibition of inflammatory cytokines [15,16]. However, our findings should be interpreted with caution due to the low quality of the available evidence.

At day 6–10, it was unclear whether or not the use of ivermectin compared to controls decreased the rate of patients with RT-PCT-negative test (very low quality of evidence). By contrast, at day 14, the rate of patients with negative RT-PCR test was 21% higher (from 5 to 36% higher) among ivermectin recipients, but the quality of evidence was low. An early decrease of viral load in ivermectin group compared to controls was demonstrated in the study by Samaha et al., but the authors reported the cycle threshold values of RT-PCR test and not the rate of patients with a RT-PCR-negative test; therefore, we could not pool these data with those of the studies included in the review

Results from three studies (736 subjects) showed that prophylaxis with ivermectin increased the likelihood of preventing COVID-19 compared to controls (low quality of evidence). Serious adverse events were rarely reported both in ivermectin and controls.

The quantitative analysis conducted in this systematic review has, however, several limitations that do not allow us to draw definite conclusions about the efficacy of ivermectin in this setting. An important limitation is certainly related to the heterogeneity of the studies evaluated, which encompasses both clinical and methodological heterogeneity. Differences between studies in terms of clinical factors, such as setting (i.e., outpatients and hospitalized patients), severity of COVID-19, doses and administration schedule of ivermectin and comparators, and methodological factors such as bias in the selection of patients and in the assessment and reporting of outcomes, were common. Even so, in this systematic review, we have highlighted these differences and addressed heterogeneity using a random effect model and performing subgroup analyses. Another important limitation of this review is that the assessments of ivermectin for COVID-19 continue to be published in preprints and protocol repositories, which do not follow the recommended processes to ensure high quality standards for publications [19]. As much as possible, we have minimized potential biases in the review process. We followed the methods set out in our published PROSPERO protocol, a key feature for providing transparency in the review process and to ensure protection against reporting biases, as well as structuring a summary of findings table and GRADE assessment as required by the new Cochrane standards.

Another important issue to be considered in trials with ivermectin is the drug dosage. Well-controlled dose–response studies need to be considered to carry out a clinical trial of ivermectin. Schmith et al. [45] carried out simulations with the help of a population pharmacokinetic model for predicting total and unbound plasma concentration–time profiles of ivermectin after administration of the approved dose (200 μg/kg,) or much higher doses (60 mg, and 120 mg), in single and repeated doses. According to these results, the IC_{50} value of ivermectin is much higher than the maximum plasma concentration achieved after administration of the above-mentioned three doses of ivermectin [46], and, as a consequence, the chances of success of a trial using the approved ivermectin dose (200 μg/kg) is low. Indeed, after daily dosing of ivermectin 200 μg/kg, lung concentrations are predicted to be around 1/4th of the IC_{50}. On the other hand, it is also conceivable that the

in vitro findings do not correlate with in vivo findings, and that concentrations of the drug in lung tissue do not need to reach the IC_{50} for clinical benefit [13,44].

In this review, we carried out a subgroup analysis, according to the dose of ivermectin administered, the approved 200 μg/kg dose, or a 400 μg/kg dose: in neither case were there differences in the mortality rate between ivermectin recipients and controls. There is some evidence that ivermectin is safe, even at higher doses and frequency regimens [46]. Doses of ivermectin such as 120 mg (up to 2000 μg/kg) taken once or at 180 mg (up to 3000 μg/kg) in split doses over 1 week are well-tolerated and safe [47]. It would be important to conduct a well-controlled clinical dose–response study with ivermectin at the approved dose and at a higher dose in relation to placebo in patients with COVID-19. Moreover, future studies might consider new formulations, such as aerosolized and parenteral ivermectin.

The latest version of the WHO living guidance and IDSA guidelines recommends against ivermectin in patients with COVID-19 regardless of disease severity, except in the context of a clinical trial [48,49]. More studies are underway, and it would be premature to conclude that ivermectin has no place in COVID-19 treatment. However, as our systematic review confirms, further evidence is needed to better define potential indications and optimal treatment protocols for ivermectin as a treatment of COVID-19.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/diagnostics11091645/s1, PRISMA checklist. Table S1. Characteristics of studies and risk of bias. Table S2. Data and analysis. Figure S1. Risk of bias graphs. Figure S2. Forest plot. Mortality according to ivermectin dose (high dose, 400 μg/kg, or standard dose, 400 μg/kg). Figure S3. Forest plot. Outcome: overall adverse events and serious adverse events. Figure S4. Forest plot. Outcome: ivermectin prophylaxis, overall rate of COVID-19 infection in contacts. Figure S5. Forest plot. Outcome: ivermectin prophylaxis, rate and severity of COVID-19 infection in contacts.

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